Exhibit II

the target concentration is 15 mg per liter, and this is attained at a dosing rate of 300 mg per day, then, from equation 1–15, v_m equals 320 mg per day. For such a patient, a dose 10% less than optimal (*i.e.*, 270 mg per day) will produce a C_{ss} of 5 mg per liter, well below the desired value. In contrast, a dose 10% greater than optimal (330 mg per day) will exceed metabolic capacity (by 10 mg per day) and cause a long and slow but unending climb in concentration until toxicity occurs. Dosage cannot be controlled so precisely (less than 10% error). Therefore, for those patients in whom the target concentration for phenytoin is more than tenfold greater than the K_m, alternating inefficacious therapy and toxicity is almost unavoidable.

Design and Optimization of Dosage Regimens

When long-term therapy is initiated, a pharmacodynamic question must be asked: What degree of drug effect is desired and achievable? If some effect of the drug is easily measured (*e.g.*, blood pressure), it can be used to guide dosage, and a trial-and-error approach to optimal dosage is both practical and sensible. Even in this ideal case, certain quantitative issues arise, such as how often to change dosage and by how much. These usually can be settled with simple rules of thumb based on the principles discussed (*e.g.*, change dosage by no more than 50% and no more often than every three to four half-lives). Alternatively, some drugs have very little dose-related toxicity, and maximum efficacy is usually desired. For these drugs, doses well in excess of the average required will both ensure efficacy (if this is possible) and prolong drug action. Such a "maximal dose" strategy typically is used for penicillins and most β-adrenergic blocking agents.

Target Level. For some drugs, the effects are difficult to measure (or the drug is given for prophylaxis), toxicity and lack of efficacy are both potential dangers, and/or the therapeutic index is narrow. In these circumstances doses must be titrated carefully, and a target-level strategy is reasonable. A desired (target) steady-state concentration of the drug (usually in plasma) is chosen, and a dosage is computed that is expected to achieve this value. Drug concentrations are subsequently measured, and dosage is adjusted if necessary to approximate the target more closely (*see also* Chapter 3).

To apply the target-level strategy, the therapeutic objective must be defined in terms of a desirable range for the C_{ss}, often called the therapeutic range. For drugs for which this can be done, such as theophylline and digoxin, the lower limit of the therapeutic range appears to be approximately equal to the drug concentration that produces about half of the greatest possible therapeutic effect. The upper limit of the therapeutic range (for drugs with such a limit) is fixed by toxicity, not by efficacy. In general, the upper limit of the therapeutic range is such that no more than 5% to 10% of patients will experience a toxic effect. For some drugs, this may mean that the upper limit of the range is no more than twice the lower limit. Of course, these figures can be highly variable, and some patients may benefit greatly from drug concentrations that exceed the therapeutic range, while others may suffer significant toxicity at much lower values. Barring more specific information, however, the target is usually chosen as the center of the therapeutic range.

Maintenance Dose. In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion in order to maintain a steady-state concentration of drug in plasma within a given therapeutic range. Thus, calculation of the appropriate maintenance dosage is a primary goal. To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss. This relationship was defined previously in equations 1–1 and 1–14 and is expressed here in terms of the desired target concentration:

$$\text{Dosing rate} = \text{Target} \cdot CL/F \qquad (1\text{–}16)$$

If the clinician chooses the desired concentration of drug in plasma and knows the clearance and availability for that drug in a particular patient, the appropriate dose and dosing interval can be calculated.

Example. A steady-state plasma concentration of theophylline of 15 mg per liter is desired to relieve acute bronchial asthma in a 68-kg patient. If the patient does not smoke and is otherwise normal except for the asthmatic condition, one can use the mean clearance given in Appendix II, that is, 0.65 ml $\cdot$ min^{-1} $\cdot$ kg^{-1}. Because the drug is to be given as an intravenous infusion, $F = 1$:

$$\begin{aligned}\text{Dosing rate} &= \text{Target} \cdot CL/F \\ &= 15\ \mu\text{g/ml} \cdot 0.65\ \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &= 9.75\ \mu\text{g} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &= 40\ \text{mg/h for a 68-kg patient}\end{aligned}$$

Since almost all intravenous preparations of theophylline are available as the ethylenediamine salt (aminophylline), which contains 85% theophylline, the infusion rate will be 47 mg per hour of aminophylline [(40 mg per hour)/(0.85)].

Dosing Interval for Intermittent Dosage. In general, marked fluctuations in drug concentrations between doses are not beneficial. If absorption and distribution were instantaneous, fluctuation of drug concentrations between doses would be governed entirely by the drug's elimination half-life. If the dosing interval (T) was chosen to

be equal to the half-life, then the total fluctuation would be twofold; this is usually a tolerable variation.

Pharmacodynamic considerations modify this. If a drug is relatively nontoxic, such that concentrations many times that necessary for therapy can be tolerated easily, the maximal dose strategy can be used, and the dosing interval can be much longer than the elimination half-life (for convenience). The half-life of penicillin G is less than 1 hour, but it is often given in very large doses every 6 or 12 hours.

For some drugs with a narrow therapeutic range, it may be important to estimate the maximal and minimal concentrations that will occur for a particular dosing interval. The minimal steady-state concentration $C_{ss,min}$ may be reasonably determined by the use of equation 1–17:

$$C_{ss,min} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} \cdot exp(-kT) \qquad (1\text{–}17)$$

where k equals 0.693 divided by the clinically relevant plasma half-life and T is the dosing interval. The term $exp(-kT)$ is, in fact, the fraction of the last dose (corrected for bioavailability) that remains in the body at the end of a dosing interval.

For drugs that follow multiexponential kinetics and that are administered orally, the estimation of the maximal steady-state concentration $C_{ss,max}$ involves a complicated set of exponential constants for distribution and absorption. If these terms are ignored for multiple oral dosing, one may easily predict a maximal steady-state concentration by omitting the $exp(-kT)$ term in the numerator of equation 1–17 (*see* equation 1–18, below). Because of the approximation, the predicted maximal concentration from equation 1–18 will be greater than that actually observed.

Example. When the acute asthmatic attack in the patient discussed above is relieved, the clinician might want to maintain the plasma concentration of theophylline at 15 mg per liter, with oral dosage at intervals of 6, 8, or 12 hours. The correct rate of drug administration, independent of consideration of the dosing interval, is 40 mg per hour for this patient, as calculated above, since the availability of theophylline from an oral dose is 100%. Thus, the appropriate intermittent doses would be 240 mg every 6 hours, 320 mg every 8 hours, or 480 mg every 12 hours. All of these regimens would yield the same average concentration of 15 mg per liter, but different maximal and minimal concentrations would obtain. For a 12-hour dosing interval, the following maximal and minimal concentrations would be predicted:

$$C_{ss,max} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} = \frac{480 \text{ mg}/34 \text{ liters}}{0.65} = 21.7 \text{ mg/liter} \qquad (1\text{–}18)$$

$$C_{ss,min} = C_{ss,max} \cdot exp(-kT) = (21.7 \text{ mg/liter}) \cdot (0.35) = 7.6 \text{ mg/liter} \qquad (1\text{–}19)$$

The calculations in equations 1–18 and 1–19 were performed assuming oral doses of 480 mg every 12 hours of a drug with a half-life of 8 hours ($k = 0.693/8 \text{ h} = 0.0866 \text{ h}^{-1}$), a volume of distribution of 0.5 liter/kg (V_{ss} = 34 liters for a 68-kg patient), and an oral availability of 1. Since the predicted minimal concentration, 7.6 mg per liter, falls below the suggested effective concentration and the predicted maximal concentration is above that suggested to avoid toxicity (*see* Appendix II), the choice of a 12-hour dosing interval is probably inappropriate. A more appropriate choice would be 320 mg every 8 hours or 240 mg every 6 hours; for T = 6 h, $C_{ss,max}$ = 17 mg per liter; $C_{ss,min}$ = 10 mg per liter. Of course the clinician must balance the problem of compliance with regimens that involve frequent dosage against the problem of periods when the patient may be subjected to concentrations of the drug that could be too high or too low.

Loading Dose. The "loading dose" is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. The appropriate magnitude for the loading dose is:

$$\text{Loading dose} = \text{Target } C_p \cdot V_{ss}/F \qquad (1\text{–}20)$$

A loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated. For example, the half-life of lidocaine is usually more than 1 hour. Arrhythmias encountered after myocardial infarction obviously may be life threatening, and one cannot wait 4 to 6 hours to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to maintain this concentration. Hence, use of a loading dose of lidocaine in the coronary care unit is standard.

The use of a loading dose also has significant disadvantages. First, the particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug. Moreover, if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved was excessive. Loading doses tend to be large, and they are often given parenterally and rapidly; this can be particularly dangerous if toxic effects occur as a result of actions of the drug at sites that are in rapid equilibrium with plasma.

Individualizing Dosage. To design a rational dosage regimen, the clinician must know F, CL, V_{ss}, and $t_{1/2}$, and have some knowledge about rates of absorption and distribution of the drug. Moreover, one must judge what variations in these parameters might be expected in a particular patient. Usual values for the important parameters and appropriate adjustments that may be necessitated by disease or other factors are presented in Appendix II. There is, however, unpredictable variation among normal individuals; for many drugs, one standard deviation in the values observed for F, CL, and V_{ss} is about 20%, 50%, and 30%, respectively. This means that 95% of the time the C_{ss}

that is achieved will be between 35% and 270% of the target; this is an unacceptably wide range for a drug with a low therapeutic index. If values of C_p are measured, one can estimate values of F, CL, and V_{ss} directly, and this permits more precise adjustment of a dosage regimen. Such measurement and adjustment are appropriate for many drugs with low therapeutic indices (*e.g.*, cardiac glycosides, antiarrhythmic agents, anticonvulsants, theophylline, and others).

Therapeutic Drug Monitoring

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of CL/F for the patient being treated (using equation 1–14 as rearranged below):

$$CL/F \text{ (patient)} = \text{Dosing rate}/C_{ss} \text{ (measured)} \qquad (1\text{–}21)$$

The new estimate of CL/F can be used in equation 1–16 to adjust the maintenance dose to achieve the desired target concentration.

Certain practical details and pitfalls related to therapeutic drug monitoring should be kept in mind. The first of these concerns the time of sampling for measurement of the drug concentration. If intermittent dosing is used, when during a dosing interval should samples be taken? It is necessary to distinguish between two possible uses of measured drug concentrations in order to understand the possible answers. A concentration of drug measured in a sample taken at virtually any time during the dosing interval will provide information that may aid in the assessment of drug toxicity. This is one type of therapeutic drug monitoring. It should be stressed, however, that such use of a measured concentration of drug is fraught with difficulties because of interindividual variability in sensitivity to the drug. When there is a question of toxicity, the drug concentration can be no more than just one of many items that serve to inform the clinician.

Changes in the effects of drugs may be delayed relative to changes in plasma concentration because of a slow rate of distribution or pharmacodynamic factors. Concentrations of digoxin, for example, regularly exceed 2 ng/ml (a potentially toxic value) shortly after an oral dose, yet these peak concentrations do not cause toxicity; indeed, they occur well before peak effects. Thus, concentrations of drugs in samples obtained shortly after administration can be uninformative or even misleading.

When concentrations of drugs are used for purposes of adjusting dosage regimens, samples obtained shortly after administration of a dose are almost invariably misleading. The point of sampling during supposed steady state is to modify one's estimate of CL/F and thus one's choice of dosage. Early postabsorptive concentrations do not reflect clearance; they are determined primarily by the rate of absorption, the central (rather than the steady-state) volume of distribution, and the rate of distribution, all of which are pharmacokinetic features of virtually no relevance in choosing the long-term maintenance dosage. When the goal of measurement is adjustment of dosage, the sample should be taken well after the previous dose—as a rule of thumb just before the next planned dose, when the concentration is at its minimum. There is an exception to this approach: some drugs are nearly completely eliminated between doses and act only during the initial portion of each dosing interval. If, for such drugs, it is questionable whether efficacious concentrations are being achieved, a sample taken shortly after a dose may be helpful. Yet, if another concern is that low clearance (as in renal failure) may cause accumulation of drug, concentrations measured just before the next dose will reveal such accumulation and are considerably more useful for this purpose than is knowledge of the maximal concentration. For such drugs, determination of both maximal and minimal concentrations is thus recommended.

A second important aspect of the timing of sampling is its relationship to the beginning of the maintenance dosage regimen. When constant dosage is given, steady state is reached only after four half-lives have passed. If a sample is obtained too soon after dosage is begun, it will not accurately reflect clearance. Yet, for toxic drugs, if one waits until steady state is ensured, the damage may have been done. Some simple guidelines can be offered. When it is important to maintain careful control of concentrations, one may take the first sample after two half-lives (as calculated and expected for the patient), assuming no loading dose has been given. If the concentration already exceeds 90% of the eventual expected mean steady-state concentration, the dosage rate should be halved, another sample obtained in another two (supposed) half-lives, and the dosage halved again if this sample exceeds the target. If the first concentration is not too high, one proceeds with the initial rate of dosage; even if the concentration is lower than expected, one usually can await the attainment of steady state in another two estimated half-lives and then proceed to adjust dosage as described above.

If dosage is intermittent, there is a third concern with the time at which samples are obtained for determination of drug concentrations. If the sample has been obtained just prior to the next dose, as recommended, concentration will be a minimal value, not the mean. However, as discussed above, the estimated mean concentration may be calculated by using equation 1–14.

If a drug follows first-order kinetics, the average, minimum, and maximum concentrations at steady state are linearly related to dose and dosing rate (*see* equations 1–14, –17, and –18). Therefore, the ratio between the measured and the desired concentrations can be used to adjust the dose:

$$\frac{C_{ss}(\text{measured})}{C_{ss}(\text{desired})} = \frac{\text{Dose(previous)}}{\text{Dose(new)}} \qquad (1\text{–}22)$$

Finally, for some drugs that are particularly difficult to manage, computer programs may be useful for the design of dosage regimens. Such programs, which take into account measured drug concentrations and individual factors such as those listed in Appendix II, are becoming increasingly available (Gabrielsson and Weiner, 1994).